Book Review

Rational Molecular Design in Drug Research, *Alfred Benzon Symposium No. 42. Edited by T. Liljefors, F. S. Jorgensen, and P. Krogsgaard–Larsen, Munksgaard, Copenhagen, 1998, 399 pp. ISBN 87-16-12049-3.*

This book is a symposium proceedings volume, and it exhibits many of the typical strengths and weaknesses of such publications; however, I am pleased to report that the strengths clearly outweigh the weaknesses in this case. The Alfred Benzon Symposium No. 42 brought together a genuinely outstanding group of scientists who work in the general areas of computational chemistry and biomolecular design; thus, the proceedings are valuable as documentation of the state of the art in this exciting field in 1997.

The collection begins with an overview by Donald Boyd that, among other things, is notable for having an up to date answer to the perennial question of which specific marketed drugs can be listed as ''success stories'' for rational molecular design. (For those who cannot wait to get the book, in addition to the well-known HIV protease inhibitors, some of the other examples mentioned by Boyd include the antibiotic norfloxacin, the carbonic anhydrase inhibitor dorzolamide, the antimigraine agent zolmitriptan, and the acetylcholinesterase inhibitor donepezil.)

Each chapter is followed by a transcript of the discussions that ensued after the corresponding presentation; actually, these are a very nice feature of the book, because the quality of the questions is remarkably good and many points about which the reader might also wonder are raised and generally well answered in these discussions.

The articles are grouped in four major sections, corresponding to the two extreme cases involving ligand design for structurally unknown binding sites (Section I, 3D-QSAR, etc.) versus ligand design for structurally known binding sites (Section IV, Structure-Based Ligand Design) with two other sections interspersed: one on molecular similarity and diversity (Section II) and one on ligand–protein interactions (Section III). In this brief review it is not possible to mention all of the articles included in the book, but an outline of some representative contents is in order.

Section I includes an excellent overview of selective peptidomimetic ligand design from Victor Hruby's group, which is exemplified for δ-selective opioid receptor ligands. Although it is a somewhat unusual case because of an almost exclusive focus on side chain rather than backbone conformation, it is an elegant and highly successful study.

There is only a single chapter in the book that is entirely devoted to CoMFA, but it is nonetheless a very important one because it addresses the critical question of how to obtain consistent results with this widely used 3D-QSAR method. Using a variant they call UniSurCoFMA, which computes the CoMFA field values on a grid restricted to the union dot surface of the set of aligned molecules, Kim et al. show that the consistency of CoMFA results is significantly improved; in addition, the model statistics are no longer dependent upon arbitrary factors such as orientation on the computer screen. This approach, which uses the accurate dot surface algorithm of Brusniak and Pearlman to compute the union dot surface, appears to represent an alternative and equally effective solution to this limitation of standard CoMFA as compared to the cross-validated R2-guided region selection method of Cho and Tropsha, who first pointed out this problem with standard CoMFA.

Several contributions in this section involve the relatively new approach of generating pseudoreceptor models in 3-dimensional (3-D) space around

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a set of aligned ligands for subsequent use in ligand design and derivation of 3D-QSARs. The genetically evolved receptor models method of Walters and Muhammad is an example of this approach, which is unique in its use of a genetic algorithm to optimize the choice of atom types in the pseudoreceptor model.

The inclusion of Section II on molecular similarity and diversity reflects the growing importance of computational methods in ''data base mining'' and in the design and analysis of libraries for combinatorial synthesis, a technology that has been widely embraced by the pharmaceutical industry. Contributions to this section range from fundamental studies on the definition and development of metrics for chemical diversity to a new computational technique for reducing the dimensionality of molecular structures from 3-D to 2-D without loss of distance information from the 3-D structure. The latter method, which is described in an article by Richards and Robinson, may be significant for various protein structure studies, as well as for the general problem of assessment of molecular similarity.

Advances in computational methods for the study of ligand–protein interactions are essential for the continued development of the more applied area of structure-based drug design. Section III focuses on the former and begins with a useful overview by J. Andrew McCammon about the advances in molecular dynamics simulation methods and applications. This is followed by an ambitious example of a quantum mechanical study of a ligand–receptor interaction by Folkers et al. who use density functional theory calculations to study a highly simplified receptor model derived from the crystal structure of thymidine kinase.

The GRID program was one of the earliest methods devised to predict potential ligand binding sites on molecules, using a probe atom approach; a report by Goodford describes new capabilities of version 15 of GRID, including the ability to treat certain side chains in the target as flexible.

Other articles in Section III cover topics such as conformational analysis using molecular dynamics and calculation of conformational energies of bound ligands.

The final section is a collection of studies in basic and applied structure-based drug design, and there are a total of seven articles plus a concluding overview by Klaus Müller. The biological activities of the macromolecular targets covered in the various articles include G-protein coupled receptors, various bacterial and viral proteins, and class II MHC proteins. Of course, HIV protease inhibitors are one of the major success stories of rational drug design, and they are represented here in a detailed report by Lam et al.

Several methods-oriented articles in this section are of particular interest. The contribution by Bohacek et al. describes results obtained using GrowMol, a *de novo* ligand design program that is notable for having produced a number of known high affinity ligands as output, as well as structures very similar to known ligands. Most exciting is the fact that the method has led to the identification of active compounds that have no structural similarity to known ligands, and thus are genuinely new lead compounds.

The contribution from Marshall and Kisselev is also noteworthy, because they describe promising successes in predicting actual binding affinities by means of heuristic approximations of the entropy of binding within a series of related molecules. They also provide an example of the determination of the conformation of a bound ligand even when the explicit receptor structure is not known.

The book ends with perspectives on structure-based drug design in the industrial setting by Mark Murko et al. from Vertex Pharmaceuticals (which includes another HIV protease inhibitor design story), and the final perspective by Klaus Müller from Hoffman–LaRoche. The latter sounds a note of realism at the end, pointing out that the evolution of modern pharmaceutical research practice suggests that molecular modeling is ''no longer in the driver's seat of lead optimization, but rather in the role of driver's mate.''

This book will be of considerable interest to anyone who desires to gain insight into the current thinking and methods of many of the leading researchers in biomolecular design. However, its potential utility as a graduate textbook may be somewhat limited because of two factors. First, because presentations at symposia tend to focus on the latest developments, such proceedings volumes are generally inconsistent in regard to the inclusion of chapters covering the fundamental aspects required to provide a broad base in the subject; this volume is no exception, and the format does not seem to have been designed with use as a textbook in mind. Furthermore, because the length of the articles is somewhat constrained, the level of technical detail that is included is generally less than what is usual for comparable re-

search articles or what might be required for a student to implement the various methods. Such material can nonetheless be gleaned from previous publications cited in most of the articles. However, for an advanced or second semester graduate course in molecular modeling methods, this book would be of value because of its comprehensive coverage of current developments relevant to the highest level of research practice in this field.

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